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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

TONGUE, LAKIA J

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/644,927

Applicant(s)

STERN ET AL.

Examiner

Lakia J. Tongue

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 3-5, 7 and 9-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 6, 8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

In a response to an Election/Restriction Requirement filed on 4/08/05 applicant elected with traverse Group I, Claims 1-11 drawn to an isolated bacteriocin produced by a lactic acid producing bacteria. Applicant has further elected SEQ ID NO 1 and corresponding NRRL B-30514 as the single specie. Claims 12-34 are withdrawn as they are drawn to nonelected subject matter. Claims 3-5, 7 and 9-11 are withdrawn as they are drawn to non-elected species. Claims 1, 2, 6 and 8 are under examination. Applicant's election with traverse of Group I claims 1-11 in the reply filed on 4/8/05 is acknowledged. The traversal is on the ground(s) that the invention must be independent or distinct as claimed and there must be a serious burden on the examiner if restriction is not required. This argument has been considered, but not found persuasive. MPEP § 808.02 recites that for the purposes of the initial requirement of a restriction, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02. Since the Examiner has shown a different classification for the three groups of claims, a burden for examining all groups together has been shown.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 8/21/03 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the information disclosure statement. However, there are additional references in the specification which do not appear on the information disclosure statement. Those references need to be on the IDS, thus, unless the examiner on form PTO-892 has cited the references, they have not been considered.

Specification

2. The disclosure is objected to because of the following informalities: the recitations are incomplete. Each recitation should include the author, source, date of publication, volume, issue number and pages.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1,2,6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1,2,6 and 8 are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of a strain selected from the group consisting of NRRL B-30514, NRRL B-30510, NRRL B-30511 and NRRL B-30645.

Because it is not clear that cell lines possessing the properties of **Lactobacillus salivarius NRRL B-30514 (Strain PVD32)**, **Lactobacillus acidophilus NRRL B-30510 (Strain LWP320)**, **Enterococcus durans NRRL-B30511 (Strain LWP26)** and **Enterococcus faecalis NRRL B-30645 (Strain LWP21)** are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of a suitable deposit for patent purposes a deposit in a public repository is required. Without a publicly available deposit of the above **Lactobacillus salivarius NRRL B-30514 (Strain PVD32)**, **Lactobacillus acidophilus NRRL B-30510 (Strain LWP320)**, **Enterococcus durans NRRL-B30511 (Strain LWP26)** and **Enterococcus faecalis NRRL B-30645 (Strain LWP21)**, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the deposit of **Lactobacillus salivarius NRRL B-30514 (Strain PVD32)**, **Lactobacillus acidophilus NRRL B-30510 (Strain LWP320)**, **Enterococcus durans NRRL-B30511 (Strain LWP26)** and **Enterococcus faecalis NRRL B-30645 (Strain LWP21)** on page 15 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

Art Unit: 1645

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. The repository may test viability. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

- 1) The name and address of the depository;
- 2) The name and address of the depositor;
- 3) The date of deposit;
- 4) The identity of the deposit and the accession number given by the depository;
- 5) The date of the viability test;
- 6) The procedures used to obtain a sample if test is not done by the depository; and
- 7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the **Lactobacillus salivarius NRRL B-30514 (Strain PVD32)**, **Lactobacillus acidophilus NRRL B-30510 (Strain LWP320)**, **Enterococcus durans NRRL-B30511 (Strain LWP26)** and **Enterococcus faecalis NRRL B-30645 (Strain LWP21)** described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1,2,6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of a strain selected

from the group consisting of NRRL B-30514, having SEQ ID NO: 1, does not reasonably provide enablement for a bacteriocin having an amino acid sequence of SEQ ID NO 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of a strain selected from the group consisting of NRRL B-30514, NRRL B-30510, NRRL B-30511 and NRRL B-30645. The examiner is interpreting the claim "bacteriocin of claim 1 having an amino acid sequence of SEQ ID NO 1" which encompass having fragments of SEQ ID NO 1.

There is no guidance provided as to which amino acids can be deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of

Art Unit: 1645

polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may be changed, wherein the bacteriocin would maintain the identifying characteristics of a strain selected from the cited group. The claims broadly teach any amino acid sequence of SEQ ID NO 1, which include substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, and substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein Structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as

Art Unit: 1645

introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

There is no guidance provided in the specification as to how one would begin to choose "an amino acid sequence of SEQ ID NO 1". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what modifications can be made which would retain the biological activity of the intact protein; and
- the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The state of the art with respect to a modification of a sequence has been burdensome. Kumar, V. et al (Amino acid variations at a single residue in an autoimmune peptide profoundly affect its properties: T-cells activation, major

Art Unit: 1645

histocompatibility complex binding, and ability to block experimental allergic encephalomyelitis, Immunology, 1990; 87: 1337-1341) "shows that most substitutions in at position 4 in the N-terminal encephalitogenic MBP peptide can dramatically alter the ability of variant peptides to activate T cells and to bind to the I-A moleculesubstitutions appear to increase the ability of the peptide to bind to the MHC molecule, others fail to generate an effective immune response *in vivo* (page 1340)".

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to the modification of sequences having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are fragments or epitopes in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See *Amgen Inc v Chugai Pharmaceutical Co Ltd*. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Exparte Forman*, 230 U.S. P.Q. 546(Bd. Pat. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1,2,6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Kanatani, K. et al (Isolation and characterization of Acidocin A and cloning of the bacteriocin gene from *Lactobacillus acidophilus*, Applied and Environmental Microbiology, 1995; 61(3): 1061-1067).

Claims 1,2,6 and 8 are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of strain NRRL B-30514.

Kanatani et al disclose bacteriocin produced by *Lactobacillus Acidophilus*, which is active against closely related lactic acid bacteria (page 1061). The microorganisms disclosed in the instant specification are characterized by their anti-bacterial properties

Art Unit: 1645

(page 6, 0007). The microorganism disclosed in the prior art is known to display antimicrobial activity (page 1061). In addition Kanatani et al disclose in Fig. 3 the deduced amino acid sequence, which is identical to an amino acid sequence of instantly claimed SEQ ID NO 1 (page 1064). Inherently, the bacteriocin produced by *Lactobacillus Acidophilus* would have identifying characteristics of the claimed bacterial strain.

6. Claims 1,2,6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Robredo, B. et al, Bacteriocin production by *Lactobacillus salivarius* of animal origin, Journal of Clinical Microbiology, 2000; 38(10): 3908-09).

Claims 1,2,6 and 8 are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of strain NRRL B-30514.

Robredo et al disclose that bacteriocins are secreted oligopeptides, proteins or protein complexes with antimicrobial activity against strains taxonomically related to the producer organism. Moreover, Robredo et al disclose the production of bacteriocins isolated from *Lactobacillus salivarius* (page 3908). Inherently, the bacteriocin of the prior art produced by *Lactobacillus salivarius* would have an amino acid sequence of SEQ ID NO.1 and the identifying characteristics of the claimed strain.

7. Claims 1, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ocana, V. et al (Characterization of bacteriocin-like substance produced by a vaginal

Lactobacillus salivarius strain, Applied and Environmental Microbiology, 1999; 65(12): 5631-5635).

Claims 1,2,6 and 8 are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of strain NRRL B-30514.

Ocana et al disclose bacteriocins synthesized by bacteria having a narrow spectrum of activity, having the ability to inhibit a wide range gram-positive bacteria (page 5631). In addition Ocana et al disclose that *L. salivarius* was selected because of its ability to inhibit growth of microorganisms (page 5632). Inherently, the bacteriocin of the prior art produced by *Lactobacillus salivarius* would have the identifying characteristics of the claimed bacterial strain.

8. Claims 1,2,6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Collins et al (U.S. Patent Application Publication 2004/0214304 A1).

Claims 1,2,6 and 8 are drawn to an isolated bacteriocin produced by a lactic acid producing bacterial strain having the identifying characteristics of strain NRRL B-30514.

Collins et al disclose probiotic strains from *Lactobacillus salivarius*. Collins et al disclose the use of gram positive, catalase negative rod-shaped bacteria isolates (page 4, 0068). Moreover, Collins et al disclose a segment of amino acids that is identical to that of instantly claimed SEQ ID NO 1 (page 17). By all comparative data the strain of the prior art and the instantly claimed strain, absent evidence to the contrary, are the same. The strain of the prior art inherently anticipates the instantly claimed strain because by applicant's definition in the instant specification, the *Lactobacillus salivarius*

pvd32 strain is gram positive, catalase negative and pleomorphic rods (page 19, 0039). Additionally, the strain of the prior art would inherently have identifying characteristics of the claimed strain.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tomas, M. et al, Influence of pH temperature and culture media on the growth and bacteriocin production by vaginal *Lactobacillus salivarius* CRL 1328, Journal of Applied Microbiology, 2002; 93: 714-724.

Gardiner, G. et al, Comparative survival rates of human-derived probiotic *Lactobacillus paracsei* and *Lactobacillus salivarius* strains during heat treatment and spray drying, Applied and Environmental Microbiology, 2000; 66(6): 2605-16.

Woo, P. et al, Identification by 16S rRNA gene sequencing of *Lactobacillus salivarius* bacteremic cholecystitis, Journal of Clinical Microbiology, 2002; 40(1): 265-267.

Art Unit: 1645

Silva, J. et al, Bacteriocin production by spray-dried lactic acid bacteria, Letters in Applied Microbiology, 2002; 34: 77-81.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J. Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


LJT


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